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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,410	11/20/2003	Roger Rozot	1016800-000557	5557

21839 7590 06/12/2007
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LANDAU, SHARMILA GOLLAMUDI	
ART UNIT	**PAPER NUMBER**
1616	
MAIL DATE	**DELIVERY MODE**
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,410	ROZOT ET AL.	
	Examiner	Art Unit	
	Sharmila Gollamudi Landau	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/26/07.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,4-7,9-12,14-16,18-23,36,38-44,46-49 and 53-60 is/are pending in the application.

4a) Of the above claim(s) 9,10,21 and 48 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 2, 4-7, 11-12, 14-16, 18-20, 22-23, 36, 38-44, 46-47, 49 and 53-60 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments and Remarks filed 3/26/07 is acknowledged. Claims 1, 2, 4-7, 9-12, 14-16, 18-23, 36, 38-44, 46-49 and 53-60 are pending in this application. Claims 9-10, 21, 48 are withdrawn.

Withdrawn Rejections

The rejection over claims 1-2, 4-7, 11-20, 23, 36, 38-40, 42, 47, 49, 57 under 35 U.S.C. 103(a) as being unpatentable over EP 1176140 is withdrawn in light of applicant's amendments and remarks.

The rejection of claims 1-2, 4-7, 11-20, 23, 36, 38-40, 42, 47, 49, 57 under 35 U.S.C. 103(a) as being unpatentable over WO 99/47545 is withdrawn in light of applicant's amendments and remarks.

The rejection of claims 43-44, 46, 59-60 under 35 U.S.C. 103(a) as being unpatentable over EP 1176140 or WO 99/47545 respectively in view of Bradbury et al (6,124,362) is withdrawn in light of applicant's amendments and remarks.

The rejection of claims 41 and 58 under 35 U.S.C. 103(a) as being unpatentable over EP 1176140 or WO 99/47545 respectively in view of Rosenbaum et al (5,443,823) is withdrawn in light of applicant's amendments and remarks.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

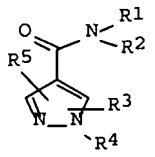
The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-7, 11-12, 14-16, 18-20, 22-23, 36, 38-44, 46-47, 49 and 53-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound 1, does not reasonably provide sufficient enablement to one of ordinary skill in the art as to which of the seemingly infinite number of derivatives disclosed across the entire scope of the extremely generic claims would in fact actually induce hair growth and hair density by inhibition of 15-PGDH, without an undue amount of experimentation. Further, the specification for enabling the treatment of alopecia, a 15-hydroxyprostaglandin-dehydrogenase disorder, does not enable the treatment of all 15-hydroxyprostaglandin dehydrogenase disorders. With regard to claim 4, while the specification enables for the reduction of 15- hydroxyprostaglandin dehydroxygenase, does not enable for the complete inhibition of hydroxyprostaglandin dehydrogenase. Therefore, the specification does not enable one skilled in the relevant art to which the invention pertains to practice (i.e., use) the invention commensurate in scope with the aforementioned rejected claims. Enablement is considered in the view of the Wands factors (MPEP 2164.01 (a)). These include the nature of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, and state of the prior art. All of the Wands factors have been considered with the regard to the instant claims, with the most relevant discussed below.

Nature of the Invention

The instant claims are directed to a method inducing hair growth and hair density and/or reducing hair growth by administering a compound with formula (I):



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Applicant attributes the growth of hair and reduction of hair loss to the inhibition of 15-PGDH by the pyrazolcarboxamide compounds.

Claim 4 is directed to a method for inhibiting 15-hydroxyprostaglandin dehydrogenase. Claim 5 is directed a method for treating a 15-hydroxyprostaglandin dehydrogenase disorder.

The Scope or Breadth of the Claims

The instant claims are directed to a method inducing hair growth and hair density and/or reducing hair growth by administering a pyrazolcarboamide compound (formula I) that is substituted with a seemingly infinite number of chemical moieties, which thereby inhibits 15-PGDH. With regard, to claim 4, the scope of the claim is directed to inhibiting 15-PGDH (inhibition entails complete inhibition). With regard to claim 5, the scope of the claim is directed to treating all 15-hydroxyprostaglandin-dihydrogenase disorder. Among disorders associated with 15-PGDH are prostate disorders including benign prostatic hypertrophy, carcinoma of the prostate, prostadynia, prostatitis, and chronic prostatitis; cancer, etc..

Guidance of the Specification

The guidance provided by the specification speaks on administering pyrazolcarboxamide compounds to induce hair growth or reducing hair loss by inhibiting 15-PGDH but does not discuss the instant structure-activity relationships with respect to how the substitution of the core with various particular chemical moieties directly effects the bioactivity and inhibitory

properties. Furthermore, the specification teaches pyrazolecarboxamides with various substituents do no have the ability of inhibiting 15-PGDH. Thus, it can readily be seen from applicant's own admission that properties of the respective compound varies with the substituents. With regard to claim 4, a method to inhibition entail completely; however Table 1 on page 67 of the instant specification demonstrates that compound 1 only inhibits 54% of 15-PGDH activity. With regard to claim 5, applicant only discloses treatment of hair loss and does not provide any guidance on treatment of prostate disorders, cancer, etc.

Working Examples

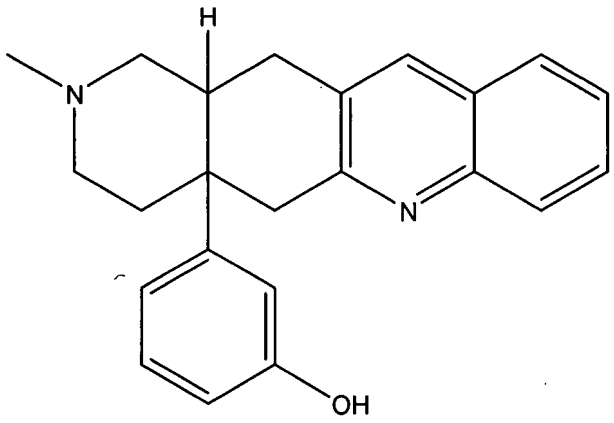
The specification exemplifies only 8 compounds out of the seemingly infinite number of derivatives claimed in the independent claims. Applicant provides an example of the inhibition of compound 1 only provides 54% inhibition.

The Level of Predictability in the Art and State of the Art

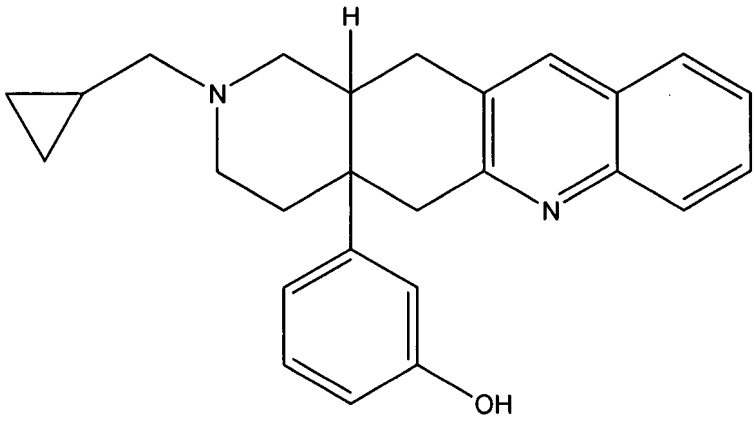
Drug discovery is an extremely tedious, laborious and expensive. The basis for the extraordinary degree of unpredictability associated with drug discovery in particular, can be attributed to the exquisite stereospecificity that exists between an enzyme and its corresponding substrate, or a ligand and its corresponding receptor. This principle is particularly evidenced by the following examples previously documented in the chemical and pharmaceutical scientific literature and prior art.

The unpredictable and surprisingly dramatic effects that can result from a simple modification of even a single pendant chemical moiety of an active core compound is strikingly apparent when considering opioid analgesics, for example. Upon simple substitution of the N-methyl group of TAN-67 (illustrated below), which is a highly selective and potent nonpeptidic δ

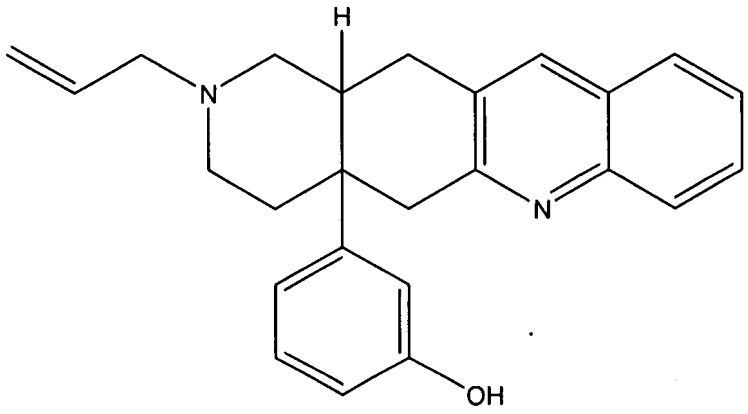
opioid receptor *agonist*, with either a methylcyclopropyl group, or even an allyl group for that matter, TAN-67 is subsequently converted into a δ opioid receptor *antagonist*. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill, NY, page 549 (1996); and Nagase, H., et al., The Pharmacological Profile of δ Opioid Receptor Ligands, (+) and (-) TAN-67 on Pain Modulation, Life Sciences, Vol. 68, pp. 2227-2231 (2001).



3-(1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol (a.k.a. TAN-67)
delta opioid receptor ***agonist***

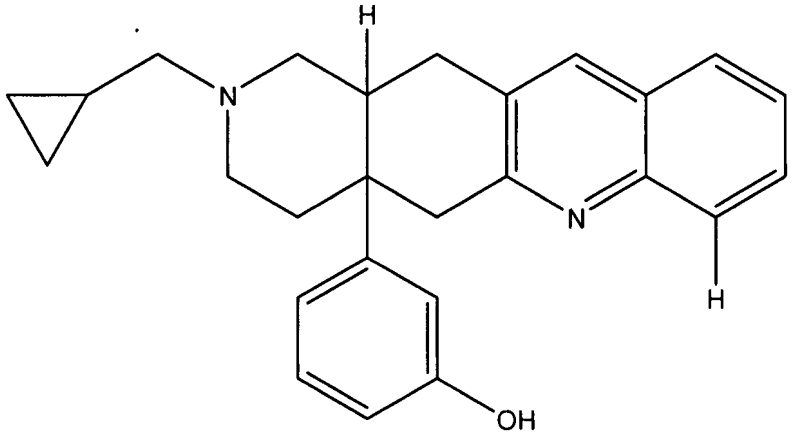


3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

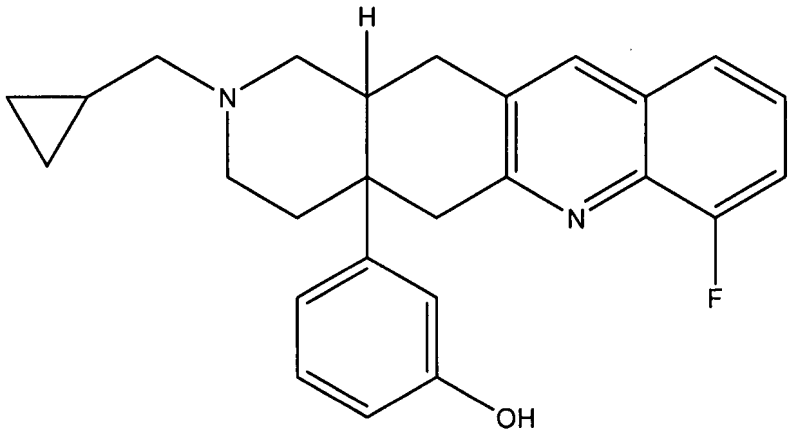


3-(2-allyl-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

In addition, if one were to modify the methylcyclopropyl substituted TAN-67, which is a δ opioid receptor *antagonist*, by substituting a fluorine atom for a hydrogen atom on the aromatic phenyl ring near the quinoline nitrogen (illustrated herein below), the δ opioid receptor *antagonist* would be converted into a *partial* δ opioid receptor *agonist*, even though fluorine and hydrogen have the same atomic radius.

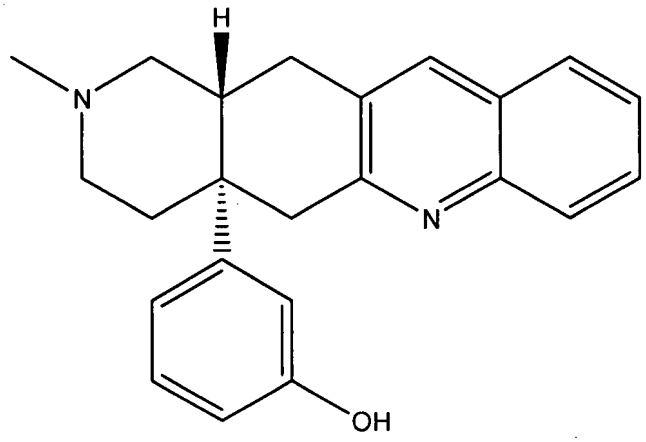


3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

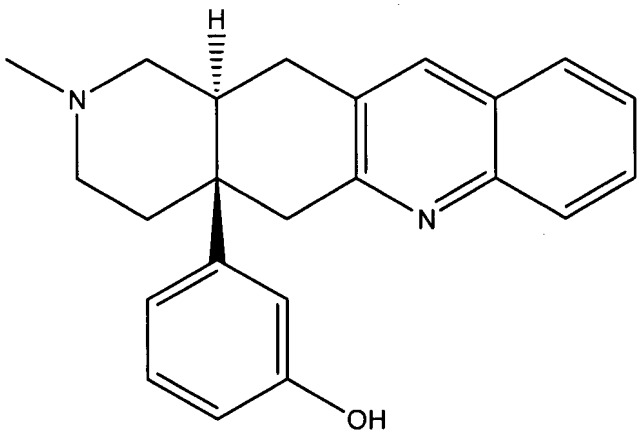


3-(2-(cyclopropylmethyl)-7-fluoro-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
partial delta opioid receptor ***agonist***

Moreover, by simply selecting from different stereoisomers of TAN-67 (illustrated below), one could go from (-)TAN-67, which is a potent antinociceptive (analgesic), to (+)TAN-67, which not only fails to exhibit analgesic properties, but astonishingly induces pain-like nociceptive behavior, such as scratching and biting.



3-((4a*S*,12a*R*)-1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol
(a.k.a. (-)TAN-67)
potent antinociceptive (analgesic)



3-((4a*R*,12a*S*)-1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol
(a.k.a. (+)TAN-67)
induces pain-like nociceptive behavior

Based on the aforementioned discussion regarding opioid analgesics, it is readily apparent that minor, seemingly trivial, modifications to the core compound can create profound changes in biological activity. The paramount and unpredictable ramifications that minor structural modifications to the core compound can have on the biological activity of opioid receptors are equally pertinent and applicable to all drugs and all receptor agonists and antagonists. Therefore, this example illustrates the exquisite stereospecific characteristics associated with all therapeutics and their reactions in vivo. Further, the example above demonstrates that a simple substitution of a halogen with a hydrogen without changing the core compound, changes the properties of the compound. In instant application, the generic broad compound claimed in the independent claim have R groups that may have varied with a broad spectrum of substituents including halogens and hydrogens. However, clearly it can be seen from the above example that a different reactivity is rendered depending on even a seemingly simple modification.

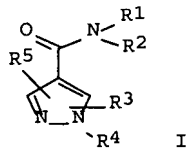
A final example evidencing unpredictability in association with drug discovery is illustrated by the following research efforts, which utilized combinatorial chemistry techniques. Combinatory chemistry is generally defined as a branch of applied chemistry concerned with the rapid synthesis and screening of large numbers of different but related chemical compounds generated from a known building block in order to recover new substances optimally suited for a specific function. In this particular example, combinatorial chemistry techniques were implemented in an effort to identify more efficacious inhibitors of cathepsin D, which is an aspartyl protease. Kick, E.K., et al., Structure-Based Design and Combinatorial Chemistry Yield Low Nanomolar Inhibitors of Cathepsin D, Chemistry & Biology, Vol. 4, No. 4, pp. 297-307

(1997). More specifically, combinatorial libraries were designed and created around the synthesis and subsequent structural derivatization of a stable mimetic building block of the tetrahedral intermediate of amide hydrolysis, namely (hydroxyethyl)amine isostere, which was an already known inhibitor of aspartyl proteases. Of the 2,000 derivatives that comprised the resultant and expansive library, over 90% of the synthesized compounds were biologically *inactive*. Since more than 90% of the synthesized compounds generated in the aforementioned combinatorial library, which was designed and created around the structural derivatization of a stable and efficacious building block or active core, were in fact biologically *inactive*, one of ordinary skill in the art would have a justifiably sound reason to doubt that even a reasonable fraction, much less a simple majority, of the chemical derivatives disclosed across the entire scope of the tremendously broad and extremely generic claims would in fact possess desired biological activity. With such a high degree of unpredictability in the drug discovery art, the applicant bears a greater burden of providing adequate support in the specification so as to guide one of ordinary skill in the art through the generic maze that is commensurate in scope with the claims.

With regard to the instant substituted pyrazolecarboxamide, The examiner further cites Bogoslovskaia SI et al. Effect of the structural characteristics of the alkyl derivatives of imidazole and pyrazole dicarboxylic acid diamides on body respiratory functions. Farmakologiia i toksikologiia, (1980 Nov-Dec) Vol. 43, No. 6, pp. 667-71. Bogoslovskaia et al disclose :

> It has been ascertained that alkyl derivatives of imidazoledicarboxylic acid diamides produce different effect on respiration and acid-base balance (ABB) of animal body. Antiphein and ethymisole stimulate respiration and change ABB. Ethirazol does not affect respiration, producing only insignificant changes in the respiratory component of ABB. Differences in the biological activity of the test drugs may be related to the structure or position of the alkyl radical in the heterocyclic ring.

The examiner cites US 5,498,624 and US 5,965,579. US '624 is directed to a pyrazolecarboxamide derivative that are useful as plant fungicides. US '579 is directed to pyrazolecarboxamide derivatives that are useful in pharmaceuticals for due to their affinity to neurotensin receptors. US 20060040950 teaches pyrazolecarboxamide derivatives that have neurokinin antagonistic activity to treat schizophrenia, anxiety, depression, etc. Thus, it can readily be seen that the properties of a compound varies with the substituents on the core. Although US '624, US '579, US '950 share the same core,



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the properties displayed by each respective compound is markedly different due to the substituents.

With regard to claim 5, Backlund et al (15-Hydroxyprostaglandin Dehydrogenase Is Down-Regulated in Colorectal Cancer, J. Biol. Chem., Vol. 280, Issue 5, 3217-3223, February 4, 2005) discloses the inhibition of 15-PDGH may suppress tumor expression. Thus, the inhibition of 15-PGDH has taught by applicant would in fact cause cancer rather than treat the carcinoma.

The Amount of experimentation Necessary

One of ordinary skill in the art would not be able to reasonably predict or anticipate the ramifications that minor structural changes, with respect to different stereoisomers of a core compound, can have on the bioactive properties thereof. Moreover, the instant application is directed to a substituted pyrazolecarboxamide and a seemingly infinite number of potential

chemical moieties without any discussion on the instant structure-activity relationships with respect to how the substitution of the core with various particular chemical moieties directly effects the bioactivity and inhibitory properties. Based on the breathtaking scope of the claimed invention and the extraordinary degree of unpredictability associated therewith, a skilled artisan would quickly become overburdened with the daunting task of attempting to accurately predict which of the countless number of derivatives, if synthesized, would actually reduce hair loss and increase hair growth by the inhibition of 15-PGDH. Without more, such as scientific data illustrating structure-activity relationships with respect to how the actual substitution of the generic pyrazolecarboxamide with various particular chemical moieties directly impacts the selective inhibition against 15-PGDH, one of ordinary skill in the art would not be able to extrapolate, without an undue amount of experimentation, which of the exponential number of derivatives disclosed across the entire breadth of the tremendously broad claims would in fact actually inhibit 15-PGDH thereby increasing hair growth. As a result, a skilled artisan seeking to practice the extraordinary scope of the claimed subject matter would be required to perform an extraordinary amount of trial and error experimentation (i.e., inhibition assays). Therefore, one of ordinary skill in the relevant art would not be able use the invention commensurate in scope with the aforementioned rejected claims.

Response to Arguments

Applicant argues that the claims have been narrowed sufficiently that encompasses the compounds of claim 22 and thus is enabled.

Applicant's arguments filed 5/25/07 have been fully considered but they are not persuasive. The examiner has provided evidence that a compound with the same core and

different substituents have vastly different properties. Moreover, the specification teaches pyrazolecarboxamides with various substituents do no have the ability of inhibiting 15-PGDH. The specification has only shown that compound 1 possesses the ability of inhibiting 15-PGDH. Thus, the examiner has sufficiently shown that is not necessarily expected that all the substituents in the Markush group will exhibit the same properties. However, applicant has not provided any evidence that substituting the core with each of the claimed Markush members would retain the property of inhibiting the 15-PGDH. Note In re Fouche, 169 USPQ 429: "Inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention; nevertheless, applicant must use some technique of providing teaching of how to use which is commensurate with breadth of protection sought by claim, unless such knowledge is already available to persons skilled in the art; thus, where applicant undertakes to define invention by recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of group."

Conclusion

All claims rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila Gollamudi Landau whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila Gollamudi Landau
Primary Examiner
Art Unit 1616

SGL